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RESEARCH ARTICLE

Ischemic patterns and their angiographic risk factors in adult patients with moyamoya disease

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Abstract

Objective: The present study aims to determine whether angiographic differences increase the risk of ischemic pattern among adult patients with moyamoya disease (MMD). **Methods**: From January 2020 to December 2021, we retrospectively enrolled 123 ischemic or asymptomatic adult patients diagnosed as MMD. Angiographic changes including Suzuki stage, moyamoya vessels, anterior choroidal artery (AChoA) dilatation, lenticulostriate artery (LSA) dilatation, posterior communicating artery (PcomA) dilatation, and posterior cerebral artery (PCA) involvement were evaluated for all patients. **Results**: Among the 123 participants, 35 ischemic patients and 88 asymptomatic patients were analyzed. There was no significant difference of Suzuki stage, AChoA dilatation, LSA dilatation, and PcomA dilatation between ischemic group and asymptomatic group. The grading of moyamoya vessels differed significantly but was not a factor associated with ischemic pattern after adjusting multiple related confounders. However, the frequency of PCA steno-occlusive changes in ischemic patients was statistically higher than that in asymptomatic patients (54.3% vs 34.1%, $p = 0.039$). Furthermore, PCA involvement was a risk factor associated with ischemic form and remained statistically significant after the multivariate adjustment ($p = 0.033$, 95% CI 1.092–8.310). **Interpretation**: PCA involvement is closely related to the presentation of ischemic stroke but other angiographic features had no association with ischemic pattern in adult MMD.

Introduction

Moyamoya disease (MMD) is characterized by chronic progressive stenosis at the terminal portions of internal carotid artery and an abnormal vascular network around the base of the brain.[1] MMD mainly affects East Asian populations such as those in Japan, Korea, and China,[2] but its etiology is still unclear. Moyamoya disease is also characterized by diverse forms of onset, clinical manifestations, and imaging features.[3] Four clinical presentations of MMD can include ischemic, hemorrhagic, epileptic, and other.[4] An ischemic event is the most common form of MMD, especially in children, in contrast to the hemorrhagic form that occur mainly in adults.[5]

Various factors have been proposed as predictors of clinical manifestations in moyamoya patients. Recent studies have demonstrated the relationship between imaging features and onset pattern, especially in hemorrhagic form. Funaki T et al suggested that the choroidal collaterals had an effect on the risk of de novo hemorrhage.[6] There was also one report showing that choroidal anastomosis was a predictor of posterior hemorrhage.[7] Additionally, some imaging factors predicting ischemic form have also been clarified. Kathuveetil A et al revealed the presence of vessel wall thickening and enhancement may predict future ischemic events in patients with MMD.[8] One study found a more severe decline of blood flow in the ischemic groups than in the asymptomatic group.[9]

Identifying the angiographic difference between ischemic form and asymptomatic type in moyamoya disease may be helpful for stroke prevention; thus, the present study aims to clarify whether angiographic differences increase the risk of ischemic stroke among adult patients with moyamoya disease.

Methods

Patients

We retrospectively collected data from patients with MMD who were hospitalized in the First Affiliated Hospital of Nanchang University from January 2020 to December 2021. Enrolled patients met the following criteria: (1) diagnosed as MMD according to the guideline proposed in 2012[10]; (2) age ≥ 18 years; (3) presented as asymptomatic form or ischemic patterns including cerebral infarction and transient ischemic attack (TIA); and (4) had no prior bypass surgery. Patients were excluded from this study if they (1) lacked angiographic, clinical, or laboratory date; (2) a term between acute ischemic stroke and angiography longer than 1 month. TIA was defined as a condition where the duration of symptoms did not exceed 24 hours, and there was no infarction through magnetic resonance imaging. Patients' clinical manifestation was evaluated by two trained neurologists. Asymptomatic MMD were defined as those who had experienced no episodes of TIA, ischemic stroke, hemorrhagic stroke, or some other neurological deficits (seizure or involuntary movement caused by MMD).[11,12] The asymptomatic MMD patients were mainly screened due to unexplained dizziness, headache, or medical check-ups. We excluded MMD-related headache which was defined in a previous study.[13] This study was approved by the Ethics Committee of the First Affiliated Hospital of Nanchang University.

Angiographic evaluation

Each patient was assessed for angiographic changes including Suzuki stage, moyamoya vessels, anterior choroidal artery (AChoA) dilatation, lenticulostriate artery (LSA) dilatation, posterior communicating artery (PcomA) dilatation, and posterior cerebral artery (PCA) involvement. Suzuki's disease stage was divided into six stages according to Suzuki's angiographical staging.[1] Basal moyamoya vessels were graded as none (grade 0), sparse (grade 1), and dense (grade 2)[14] (Fig. 1A). The dilatation of AChoA and LSA were graded according to the previously published methods: grade 0 (normal), grade 1 (dilated with distal branches), and grade 2 (dilated with abnormal branches extensions which serve blood supply to other regions)[15] (Fig. 1B,C). Additionally, the dilatation of PcomA was categorized into negative (normal or dilated perforators originating from PcomA) or positive (dilated perforators with abnormal branch extensions)[15] (Fig. 2B). Moreover, the involvement of PCA was graded as grade 0 (normal), grade 1 (stenotic), and grade 2 (occlusive)[16,17] (Fig. 2A).

Statistical analysis

All statistical analyses were performed with the use of SPSS version 26.0 (SPSS Inc., Chicago, IL, USA). We compared the baseline differences using Student's t test or Mann–Whitney U test for continuous variables and chi-square test or Fisher exact test for categorical variables. Multivariable logistic regression models were used to analyze whether moyamoya vessels or PCA involvement as a risk factor of ischemic pattern in adult MMD, adjusting all variables with $p < 0.05$ on univariate analysis and some variables reported to be associated with ischemic pattern. Significance levels were set at a $p < 0.05$ for two-tailed tests.

Results

From January 2020 to December 2021, 123 eligible patients were enrolled (35 ischemic patients and 88 asymptomatic patients). Table 1 shows the demographic, history, and laboratory characteristics between ischemic group and asymptomatic group. Compared with asymptomatic MMD, ischemic patients were older and had higher levels of creatinine. Moreover, the frequency of male and diabetes in ischemic patients were higher than those in asymptomatic patients. However, there was no significant difference in the frequency of hypertension and other laboratory data.

The baseline angiographic characteristics including Suzuki stage, moyamoya vessels, AChoA dilatation, LSA dilatation, PcomA dilatation, and PCA involvement were showed in Table 2. Among these two groups, we observed neither significant difference with respect to Suzuki stage ($p = 0.418$) and AChoA dilatation ($p = 0.631$) nor a significant relationship with respect to LSA dilatation ($p = 0.728$) and PcomA dilatation ($p = 0.577$). Moyamoya vessels in ischemic group were judged as grade 0 in 1 patient (2.86%), grade 1 in 23 patients (65.7%), and grade 2 in 11 patients (31.4%). On the other contrary, moyamoya vessels in asymptomatic group were judged as grade 0 in 7 patient (7.95%), grade 1 in 35 patients (39.8%), and grade 2 in 46 patients (52.3%). The distribution of degree of moyamoya vessel proliferation differed between the ischemic and asymptomatic groups ($p = 0.032$). In addition, the PCA involvement was graded as grade 0 ($n = 16$, 45.7%), grade 1 ($n = 9$, 25.7%), and grade 2 ($n = 10$, 28.6%) in ischemic group, but was graded as grade 0 ($n = 58$, 65.9%), grade 1 ($n = 4$, 4.55%), and grade 2 ($n = 26$, 29.5%) in asymptomatic group ($p = 0.003$). Furthermore, we divided PCA involvement into no lesions and steno-occlusive lesions and found that the prevalence of PCA steno-occlusive changes was still significantly higher than that in

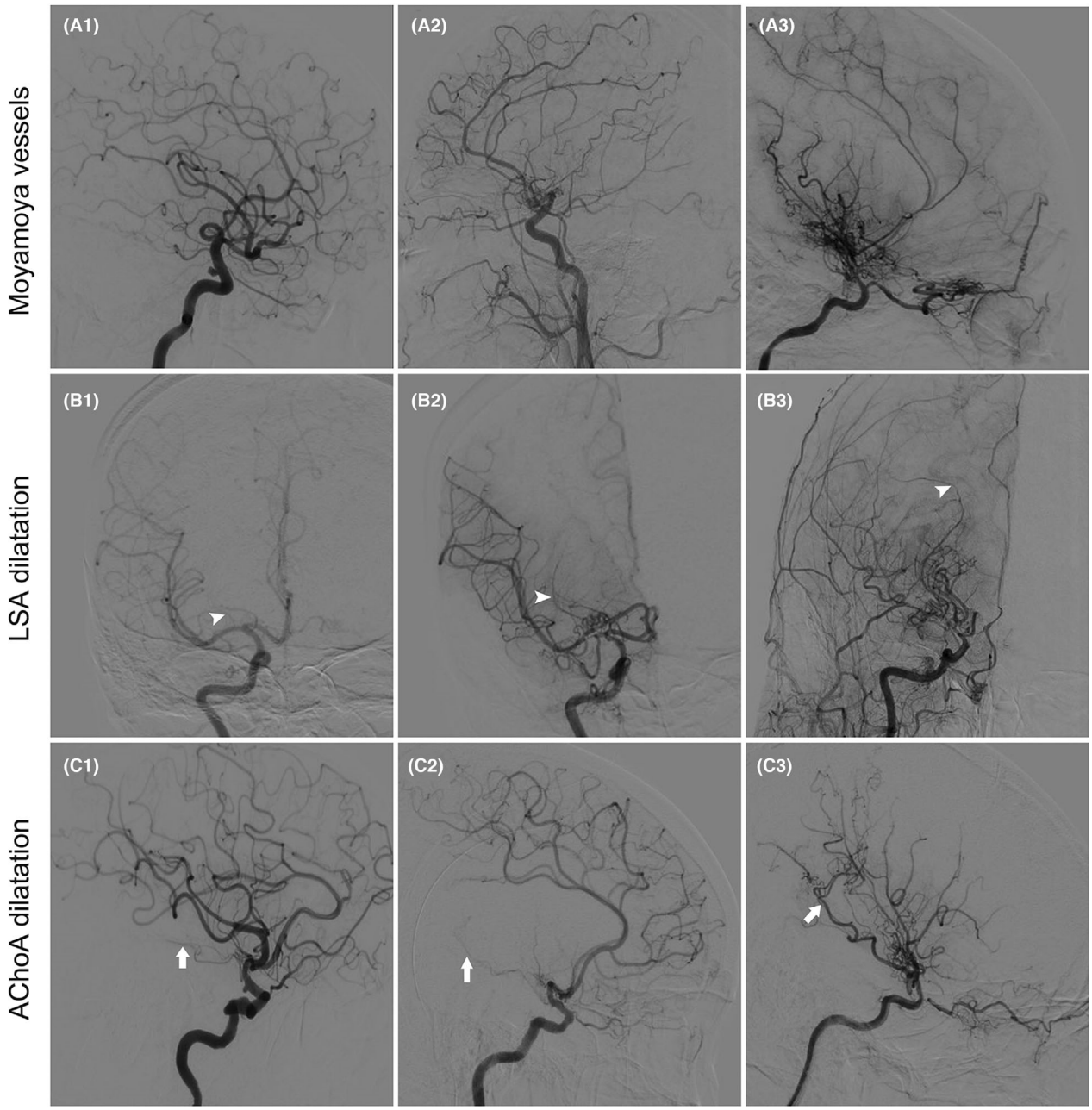

Figure 1. Representative cerebral angiography of the grading of moyamoya vessels, LSA dilatation, and AChoA dilatation. (A1–A3) Grading of moyamoya vessels: grade 0 (none, A1), grade 1 (sparse, A2), and grade 2 (dense, A3). (B1–B3) Grading of LSA dilatation (white arrowheads): grade 0 (normal, B1), grade 1 (dilated with distal branches, B2), and grade 2 (dilated with abnormal branches extensions serving blood supply to other regions, B3). (C1–C3) Grading of AChoA dilatation (white arrows): grade 0 (normal, C1), grade 1 (dilated with distal branches, C2), and grade 2 (dilated with abnormal branches extensions serving blood supply to other regions, C3).

asymptomatic patients (54.3% vs 34.1%, $p = 0.039$). What's more, a total of 29 infarct lesions coexisting with PCA involvement were further analysis, and the frequency of infarcts in anterior circulation tended to be higher than that in posterior circulation (65.5% vs 34.5%).

As shown in Table 3, multivariate logistic regression analysis revealed that the association between moyamoya vessels and ischemic pattern was not significant. In contrast, the odds ratio of PCA involvement for the risk of ischemic pattern after adjusting for age and sex was 2.41

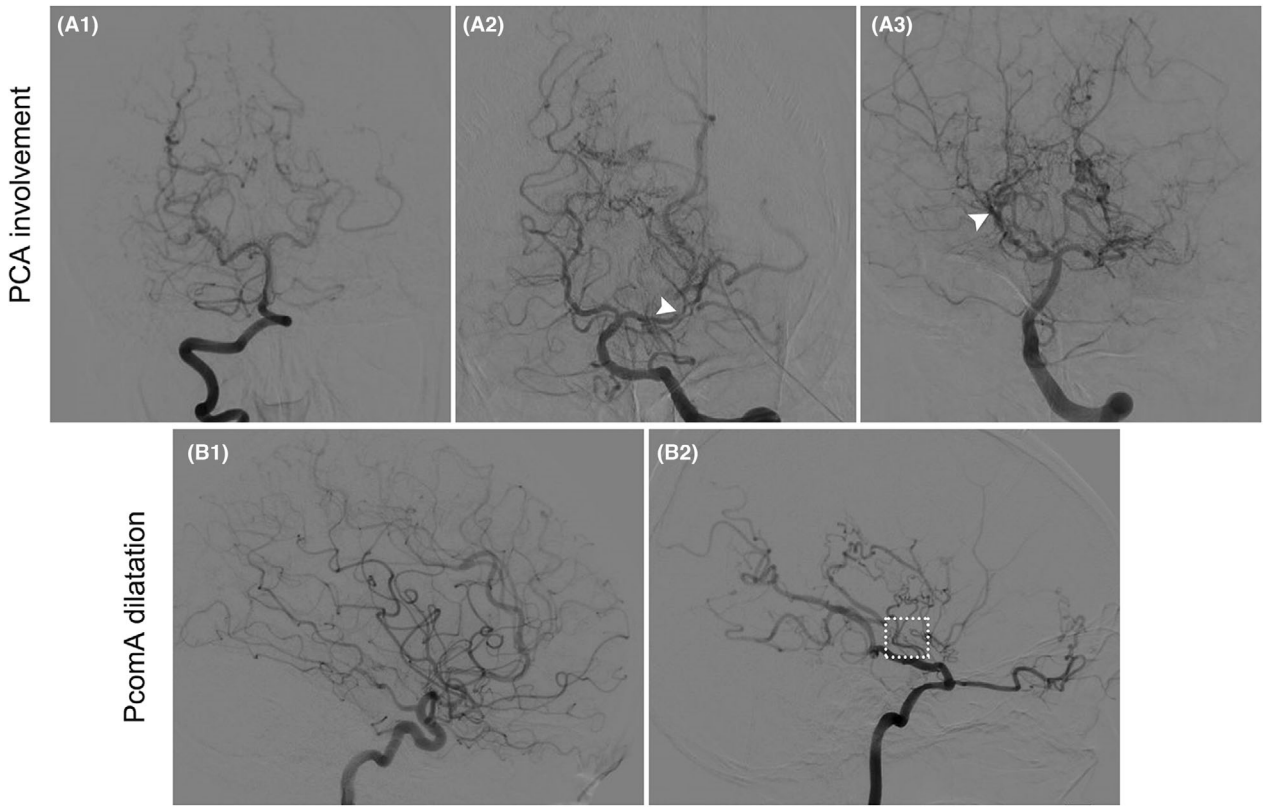

Figure 2. Representative cerebral angiography of the grading of PCA involvement and PcomA dilatation. (A1–A3) Grading of PCA involvement (white arrowheads): grade 0 (normal, A1), grade 1 (stenotic, A2), and grade 2 (occlusive, A3). (B1 and B2) Grading of PcomA dilatation (white dotted box): negative (normal or dilated perforators originating from PcomA, B1) and positive (dilated perforators with abnormal branch extensions, B2).

(Table 4, $p = 0.042$, 95% CI 1.033–5.626). After adjusting for age, male, diabetes, creatinine, and moyamoya vessels, PCA involvement was also associated ischemic form (Table 4, $p = 0.042$, 95% CI 1.033–6.445). Finally, after adjusting for multiple related confounders, namely age, male, diabetes, creatinine, moyamoya vessels, Suzuki stage, AChoA dilatation, LSA dilatation, and PcomA dilatation, PCA involvement remained significantly associated ischemic pattern (Table 4, $p = 0.033$, 95% CI 1.092–8.310).

Discussion

Our study revealed a significantly higher prevalence of PCA involvement in ischemic adult MMD patients compared to asymptomatic adult MMD patients (54.3% and 34.1%, respectively). This indicated a correlation between ischemic form and the existence of steno-occlusive PCA lesions in adult patients with MMD. However, other angiographic features (Suzuki stage, moyamoya vessels, AChoA dilatation, LSA dilatation and PcomA dilatation) had no association with ischemic manifestation in adult MMD.

In adults, nearly half of symptomatic patients with moyamoya disease presented with ischemia pattern,[2] which was related to the breakdown of compensatory cerebral blood flow. Some contributors have been reported as predictors of ischemic onset in moyamoya disease. A study had found the RNF213 c.14429G > A mutation increased the risk of cerebral ischemia at initial presentation.[18] In addition, Kim S-K et al revealed that ischemic events were significantly more frequent in children <6 years of age than those 6 years or older.[19] In terms of radiological characteristics, it was reported that the presence of steal by magnetic resonance imaging was independently associated with ischemic events.[20] However, few studies comprehensively summarized the effect of angiographic differences on ischemic pattern in MMD patients. In our study, we explored the correlation between angiographic features (Suzuki stage, moyamoya vessels, AChoA dilatation, LSA dilatation, PcomA dilatation, and PCA involvement) and ischemic pattern in adult MMD, and demonstrated that only the frequency of PCA involvement significantly increased in ischemic adult MMD patients.

Table 1. Comparison of baseline characteristics between ischemic group and asymptomatic group.

Variable	Ischemic (n = 35)	Asymptomatic (n = 88)	p
Demographic characteristics			
Age (years), mean ± SD	54.86 ± 10.04	50.59 ± 9.68	0.031*
Male, n (%)	24 (68.6%)	38 (43.2%)	0.016*
History			
Hypertension, n (%)	15 (42.9%)	28 (31.8%)	0.296
Diabetes, n (%)	9 (25.7%)	9 (10.2%)	0.045*
Laboratory data			
WBC (10^9/L), median (IQR)	6.44 (4.55, 8.51)	5.60 (4.80, 6.28)	0.105
RBC (g/L), median (IQR)	4.56 (4.07, 4.85)	4.44 (4.08, 4.72)	0.9
HGB (g/L), mean ± SD	129.49 ± 22.95	131.33 ± 13.16	0.657
PLT (10^9/L), mean ± SD	219.89 ± 48.26	217.33 ± 55.86	0.813
BUN (mmol/L), mean ± SD	4.42 ± 1.17	4.37 ± 1.15	0.838
Cr (μmol/L), mean ± SD	69.23 ± 18.12	59.51 ± 13.82	0.006*
Uric acid (mmol/L), mean ± SD	356.45 ± 91.30	332.50 ± 95.90	0.208
Fasting glucose (mmol/L), median (IQR)	5.30 (4.59, 6.99)	4.92 (4.54, 5.37)	0.073
Total cholesterol (mmol/L), mean ± SD	4.13 ± 0.97	4.33 ± 0.89	0.277
Triglyceride (mmol/L), median (IQR)	1.53 (0.97, 2.30)	1.30 (0.96, 1.81)	0.446
HDL-cholesterol (mmol/L), median (IQR)	1.02 (0.88, 1.31)	1.11 (0.97, 1.37)	0.169
LDL-cholesterol (mmol/L), mean ± SD	2.42 ± 0.86	2.60 ± 0.81	0.262

BUN, blood urea nitrogen; Cr, creatinine; HDL, high density lipoprotein; HGB, hemoglobin; IQR, interquartile range; LDL, low density lipoprotein; PLT, platelet; RBC, red blood cell; SD, standard deviation; WBC, white blood cell.
*$p < 0.05$.

Moyamoya vessels are proliferative and fragile collateral blood vessels supplying to the ischemic brain, which are assumed to originate from dilated perforating arteries such as LSA.[1,2,15] Moreover, AChoA and PcomA also serve the dilated perforating arteries and play an crucial role as alternative collateral channels in MMD.[1,2,15] Suzuki and Takaku categorized MMD into six stages on cerebral angiography, which was named Suzuki stage.[1] Some previous studies have shown that these imaging changes (moyamoya vessels, AChoA dilatation, LSA dilatation, PcomA dilatation) serving as collateral channels are closely related to intracranial hemorrhage in patients with MMD.[14,15,21,22] In fact, the angiographical dilatation of the AChoA, LSA, and PcomA may signal increased blood flow and hemodynamic stress in these vessels, which cause the rupture of fragile moyamoya vessels.[14] However, few studies focused on the associations between ischemic pattern and these imaging characteristics in MMD patients. A study enrolling 12 MMD patients found that cerebral ischemia was possibly associated with inadequate blood supply of the AChoA in the nonprogressive stage.[23] Therefore, in the present study, we comprehensively explored the associations between angiographical features and ischemic pattern in adult MMD patients. Although MMD patients with ischemia tended to manifest a higher grade of moyamoya vessels comparing to asymptomatic patients, the difference was not statistically significant in our study. Regarding Suzuki stage, Fujimura M et al revealed that it was significantly higher in hemorrhagic-onset patients than that in the ischemic-onset patients with MMD.[24] However, Hirano Y et al found no significant difference of Suzuki stage between ischemic MMD and asymptomatic MMD,[25] which was consistent with our findings. It is reasonable that the MMD patients with higher grade of Suzuki stage are more likely to develop cerebral ischemia. However, our study and some other studies did not show a significant difference between ischemic MMD and asymptomatic MMD, which may be explained by the fact that although the higher grade of Suzuki stage represents more severe steno-occlusive arteries, it may also lead to more abundant collateral channels in addition to moyamoya vessels.

MMD has been widely recognized as a steno-occlusive disease involving the internal carotid artery. However, the steno-occlusive changes in posterior circulation were also noted, especially the PCA. Reports on the hemorrhagic patterns and PCA involvement in MMD patients have started to increase during the past few years. Yamamoto S et al revealed that the prevalence of PCA involvement was significantly higher in hemorrhagic group than in asymptomatic group.[26] In addition, Funaki T et al found the association between PCA involvement and posterior hemorrhage.[27] Additionally, there was a report demonstrating PCA involvement was correlated with recurrence of ischemic stroke in MMD patients.[28] It is noteworthy

Table 2. Comparison of angiographic baseline characteristics for between ischemic group and asymptomatic group.

Variable	Ischemic (n = 35)	Asymptomatic (n = 88)	p
Suzuki stage			0.418
1	0 (0%)	1 (1.14%)	
2	2 (5.71%)	3 (3.41%)	
3	17 (48.6%)	34 (38.6%)	
4	8 (22.9%)	29 (32.9%)	
5	8 (22.9%)	15 (17.0%)	
6	0 (0%)	6 (6.82%)	
Moyamoya vessels			0.032*
Grade 0 (none)	1 (2.86%)	7 (7.95%)	
Grade 1 (sparse)	23 (65.7%)	35 (39.8%)	
Grade 2 (dense)	11 (31.4%)	46 (52.3%)	
AChoA dilatation			0.631
Grade 0	18 (51.4%)	47 (53.4%)	
Grade 1	13 (37.1%)	26 (29.5%)	
Grade 2	4 (11.4%)	15 (17.0%)	
LSA dilatation			0.728
Grade 0	13 (37.1%)	30 (34.1%)	
Grade 1	20 (57.1%)	48 (54.5%)	
Grade 2	2 (5.7%)	10 (11.4%)	
PcomA dilatation			0.577
Negative	35 (100%)	84 (95.5%)	
Positive	0 (0%)	4 (4.5%)	
PCA involvement			0.003*
Grade 0 (normal)	16 (45.7%)	58 (65.9%)	
Grade 1 (stenotic)	9 (25.7%)	4 (4.55%)	
Grade 2 (occlusive)	10 (28.6%)	26 (29.5%)	
PCA involvement			0.039*
Normal	16 (45.7%)	58 (65.9%)	
Steno-occlusive	19 (54.3%)	30 (34.1%)	

AChoA, anterior choroidal artery; LSA, lenticulostriate artery; PCA, posterior cerebral artery; PcomA, posterior communicating artery.
*$p < 0.05$.

Table 3. Associations between moyamoya vessels and the risk of ischemic stroke.

Moyamoya vessels	OR	95% CI	p
Adjusted model[1]			
Grade 0 (reference)			
Grade 1	3.437	0.371–31.817	0.277
Grade 2	1.28	0.131–12.504	0.832
Adjusted model[2]			
Grade 0 (reference)			
Grade 1	13.996	0.988–198.333	0.051
Grade 2	6.042	0.388–94.122	0.199
Adjusted model[3]			
Grade 0 (reference)			
Grade 1	10.538	0.381–291.655	0.165
Grade 2	4.550	0.119–173.947	0.415

AChoA, anterior choroidal artery; CI, confidence interval; Cr, creatinine; LSA, lenticulostriate artery; OR, odds ratio; PCA, posterior cerebral artery; PcomA, posterior communicating artery.
[1]Adjusted model was controlled for age, male.
[2]Adjusted model was controlled for age, male, diabetes, Cr, and PCA involvement.
[3]Adjusted model was controlled for age, male, diabetes, Cr, PCA involvement, Suzuki stage, AChoA dilatation, LSA dilatation, and PcomA dilatation.

Table 4. Associations between posterior cerebral artery involvement and the risk of ischemic stroke.

PCA involvement	OR	95% CI	p
Adjusted model[1]			
Normal			
Steno-occlusive	2.41	1.033–5.626	0.042
Adjusted model[2]			
Normal			
Steno-occlusive	2.580	1.033–6.445	0.042
Adjusted model[3]			
Normal			
Steno-occlusive	3.013	1.092–8.310	0.033

AChoA, anterior choroidal artery; CI, confidence interval; Cr, creatinine; LSA, lenticulostriate artery; OR, odds ratio; PCA, posterior cerebral artery; PcomA, posterior communicating artery.
[1]Adjusted model was controlled for age, male.
[2]Adjusted model was controlled for age, male, diabetes, Cr, and moyamoya vessels.
[3]Adjusted model was controlled for age, male, diabetes, Cr, moyamoya vessels, Suzuki stage, AChoA dilatation, LSA dilatation, and PcomA dilatation.

that clinical series on MMD have shown that PCA involvement positively correlated with the prevalence of ischemic stroke among pediatric patients. One study involving 78 young MMD patients reported that the high prevalence of ischemic stroke in patients diagnosed before 4 years of age was associated with advanced steno-occlusive lesions of the PCA.[29] Furthermore, Hishikawa T et al found that the frequency of infarction in pediatric and adult patients with PCA involvement was significantly higher than that in pediatric and adult patients without PCA involvement.[17] However, Zhao M et al demonstrated positive correlation between ipsilateral cerebral infarction and PCA involvement only in adult MMD patients but not in pediatric MMD patients.[30] In our study, we found a higher prevalence of PCA involvement in ischemic MMD adults than asymptomatic MMD adults. This may be explained by the role of PCA as collateral compensation of the anterior circulation.[31] In the early stage of MMD, the ischemic events in the anterior circulation may be related to the inadequacy of moyamoya vessels. As the PCA is steno-occlusive in the advanced stage of MMD, the decrease of leptomeningeal collateral vessels leads to the breakdown of compensation to

anterior circulation, thereby causing that infarct lesions increase and spread to a wider area.[32,33] In the present study, we found that the infarcts coexisting with PCA steno-occlusive lesions mainly located in anterior circulation. However, subsequent research requires a larger sample size to verify this finding.

Our study has some limitations. First, this was a retrospective study based on a single stroke center. Second, 123 patients were enrolled in this study but 35 patients admitted with ischemic pattern. Therefore, the sample size is a little bit small. Nevertheless, we comprehensively analyzed angiographic difference between ischemic form and asymptomatic type in adult MMD patients. Future studies should further expand the sample size to confirm these results.

Conclusions

PCA involvement is closely related to ischemic pattern in adult MMD. However, other angiographic features (Suzuki stage, moyamoya vessels, AChoA dilatation, LSA dilatation, and PcomA dilatation) had no association with ischemic form in adult patients with MMD. Thus, monitoring PCA involvement in adult patients with MMD may provide additional information to assist in managing these patients.

Author Contributions

Concept and design: SL, WZ, QC, JL; acquisition of data: LZ, CZ, DH, PF, WZ; analysis or interpretation of data: SL, DH, PF; drafting of the manuscript: SL, WZ; critical revision of the manuscript for important intellectual content: QC, JL; obtained funding: JL, DH; All authors have read and approved the final manuscript.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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